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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/631,613	HOGREFE ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69,70,72 and 74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69, 70, 72, 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/13/06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/13/2006 has been entered.

New Ground of Rejection

Claim Rejections - 35 USC § 112

The new ground of rejection is presented to address all nucleic acid polymerases supported by the specification as originally filed.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 69, 70, 72 and 74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of enhancing a nucleic acid polymerase reaction, wherein said nucleic acid polymerase is selected from the *pyrococcus* species and Vent DNA polymerase, comprising....., it does not reasonably provide enablement for a method of enhancing any nucleic acid polymerase reaction comprising any nucleic acid polymerase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (*See In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)). These factors include, but are not limited to:

I. Quantity of Experimentation Necessary

The claimed invention is drawn to a method of a method of enhancing a nucleic acid polymerase reaction comprising (a) forming a nucleic acid polymerase reaction composition comprising: (i) a nucleic acid; (ii) at least one nucleic acid polymerase, and (iii) a P45 protein, wherein the P45 protein is in monomeric, dimeric, or multimeric form, and wherein the p45 protein is produced from a cell containing a DNA construct comprising a sequence encoding polymerase enhancing factor protein P45 operably linked to an expression vector, and (b) incubating the nucleic acid polymerase reaction composition under conditions allowing a nucleic acid polymerase reaction, wherein the P45 protein enhances the nucleic acid polymerase reaction. The claims are also drawn to a method for controlling the activity of a polymerase in a nucleic acid polymerase reaction, comprising: (a) forming a nucleic acid polymerase reaction composition: (i) a nucleic acid; (ii) at least one nucleic acid polymerase, and (iii) a polymerase enhancing factor activity, wherein the polymerase enhancing factor activity changes the amount of dUTP present or generated during the reaction, and (b) incubating the nucleic acid polymerase reaction composition under conditions allowing a nucleic acid polymerase reaction, wherein changing the amount of dUTP present or generated during the reaction controls the activity of the polymerase in the polymerization reaction.

The specification at page 5 defines "a polymerase enhancing activity" as the ability to increase the rate, fidelity and/or yield of a nucleic acid polymerization reaction mediated by a nucleic acid polymerase, or to expand or alter the range of conditions under which such reaction does or may proceed. The specification broadly teaches that the term "polymerase enhancing factor (PEF)" includes purified naturally occurring polymerase enhancing factors and wholly or partially synthetic copies or active analogs thereof.

In the Summary of the Invention and Detailed Description beginning at page 5, the specification discloses that extracts of *Pfu* cells are provided that enhance the activity of *Pfu* DNA polymerase as well as human dUTPase, which enhances polymerase activity. Further the specification teaches that polymerase enhancing factor complexes such as e.g., the P300 complex from Pfu cells sample extracts, which comprises protein components namely the P50 protein and P45 protein, function to enhance the activity of polymerase. Likewise the specification discloses that other Pfu proteins having molecule weight between 42 and 60 kD alone or in combination functions to enhance polymerase activity. The examples beginning at page 20 discloses wherein polymerase enhancing factor (PEF) activity was screened in Pfu DSM 3638 cells, identified, purified or partially purified and tested for polymerase enhancing factor in replication reactions, amplification reactions, cloning and mutagenesis assays. At page 63, the specification further teach wherein the polymerases, Pwo DNA polymerase, Deep Vent polymerase, JDF3 DNA polymerase and ES4 DNA polymerase, all of which are members of the *pyroccocus* species of DNA polymerase, and Vent DNA polymerase activity were enhanced in the presence of PEF.

The specification however does not teach or describe a method of enhancing a nucleic acid polymerase reaction or method of controlling the activity of any of the numerous nucleic

acid polymerases from other bacterial species by forming a nucleic acid polymerase reaction composition comprising a nucleic acid and any of the numerous nucleic acid polymerase along with a P45 protein or a polymerase enhancing factor activity. Likewise, the specification provides no teaching wherein any extract, protein, complex, mixture or analog that may have a polymerase enhancing factor activity as claimed in claim 72 is capable of function in the method for controlling the activity of a polymerase. Nowhere in the specification is there an indication that any of the numerous nucleic acid polymerase known in the art (see prior Office Action for citation), such as e.g., Kornberg polymerase, Klenow fragment, T4 DNA polymerase, T7 DNA polymerase, Taq DNA polymerase, Micrococcal DNA polymerase, Alpha DNA polymerase, *Ecoli* RNA polymerase, SP6 RNA polymerase, T3 RNA polymerase, T7 RNA polymerase, RNA polymerase II, Poly(A) polymerase, exo-Vent polymerase and/or etc., besides Pfu DNA polymerase, is capable of being enhanced when combined in a nucleic acid polymerase composition comprising a polymerase enhancing factor P45 protein or polymerase enhancing factor activity. The specification provides no information to allow one of ordinary skill in the art to make or use the claimed method using the large number of undisclosed polymerase sequences and unlimited extracts, proteins, complexes, mixtures or analogs that may have a polymerase enhancing factor activity. In fact, the specification teaches that the presence of PEF may not enhance the yield of PCR products generated with Taq DNA polymerase which is isolated originally from the thermophilic eubacteria, *Thermus aquaticus*, thus suggesting that not all DNA polymerases are effective in the presence of the enhancing factor(s) claimed therein. Therefore, undue burden would be required of the practitioner as the invention encompasses

numerous nucleic acid molecules and protein molecules that may are may not be functional in the claimed methods.

II. Amount of Direction and Guidance and Presence and absence of working examples

The specification does not provide a method of enhancing a nucleic acid polymerase reaction by forming a nucleic acid polymerase reaction composition that bears a reasonable correlation to the entire scope of the claims. The examples beginning at 20 to page 68 lack information concerning using any nucleic acid polymerase known in the art and/or any polymerase enhancing factor activity which may comprise any and every possible extract, protein, protein complex, mixtures. There is no guidance in the specification for detecting any and every possible extract, protein, complex, mixture of proteins or analogs thereof which may or may not be functional for controlling the activity of a polymerase. Additionally, there is no direction or guidance given to substantiate what effect any nucleic acid polymerase would have in the presence of a polymerase enhancing factor P45 protein or polymerase enhancing factor activity without further experimentation for the broad scope of the claims.

III. Level of predictability or unpredictability in the art

The specification has not enabled a method of enhancing any nucleic acid polymerase or a method for controlling the activity of any polymerase in a polymerase reaction that is commensurate fully in scope. While the molecular biology techniques utilized are know in the art, it is not routine in the art to screen multitudes nucleic acid polymerase reaction compositions, to determine nucleic acid polymerase enhancing activity. Additionally, the results of any screening or modification thereof is unpredictable since a reasonable expectation of success is

limited by a lack of knowledge concerning the functionally of all of the nucleic acid molecules and protein molecules encompasses by the claimed invention. Therefore without sufficient knowledge and guidance, determining a polymerase enhancing composition as claimed is unpredictable. Thus, for all of the foregoing reasons, undue experimentation is necessary for one of skill in the art to obtain the claimed invention.

Applicant's traversal

4. Applicant traverses the rejection on the following ground: Applicant summarizes the claim rejection under 35 U.S.C 112 first paragraph. Applicant relies on the arguments filed July 15, 2005. Applicant asserts, "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue". *In re Angstadt*, 537 F 2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)". Applicant also cites MPEP 2164.01. Applicant asserts that the Examiner has not considered all the evidence related to the Wands factors in the Examiner's analysis. Applicant states that the response of July 2005 clearly asserts that the claim are enabled and specifically pointed out that the specification included working examples with several different polymerases. Applicant addresses each of the Wands Factors addressed by the Examiner and asserts that an analysis of those factors should result in a conclusion that the claims were enabled. Applicant states that the in Advisory Action, the Examiner maintains the rejections of claims 72 and 74 under 112 first paragraphs as allegedly not being enabled. Applicant traverses the rejection and reiterates that the experimentation necessary to practice the claimed methods is not undue. Applicant asserts that as noted in Wands, "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. Applicant

contends that one skilled in the art could perform routine screening to determine whether a particular polymerase fell within the scope of the claim. Applicant states that the specification provides guidance and working examples (including working examples with several different polymerases) to aid one of skill in the art in enhancing a nucleic acid polymerase reaction with a polymerase-enhancing factor. Applicant states that furthermore it was routine in the art at the time the application was filed to perform a nucleic acid polymerase reaction. Applicant states that even if one skilled in the art could not predict the outcome of adding PEF to a particular polymerase reaction comprising a particular polymerase, one could test whether or not PEF enhanced that particular polymerase reaction simply running two polymerase reactions side by side. Applicant emphasizes that those experiments could be performed in a matter of hours. Applicant asserts that furthermore, at the time of filing of the parent priority application, one could perform many different PCR reactions at the same time. Applicant cites Udy et al as evidence and states one could complete the experiment in a matter of hours bases on the teaching of Udy et al. Applicant states that thus assuming that one skilled in the art prepared two PCR reactions for each polymerase, one with PEF and one without PEF, one could test 48 different polymerase and PEF combination using a single 96-well plate. Finally, Applicant concludes that the claims are deemed enabled and request reconsideration.

Examiner's Response

5. All of the arguments have bee thoroughly reviewed and considered but are not found persuasive for the reasons that follow. In response to Applicant's arguments that the claims are enabled bases on working examples with several different polymerases, it is noted that the Examiner considered all of the working examples provided in the enablement rejection. The

Examples provided in the specification beginning at page 20 only provides support for the method being enabling for polymerases of the *pyroccocus* species (Pwo DNA polymerase, Deep Vent polymerase, JDF3 DNA polymerase and ES4 DNA polymerase) and Vent DNA polymerase (see specifically page 63). The specification however does not provide any guidance or working examples for the plethora of other polymerases known in the art and those unknown that are encompass by the claims as broadly written. The specification does not account for the lack of predictability in the art for one skilled in the art to extrapolate the results as claimed. To reiterate, the claims as written recites a "method of enhancing a nucleic acid polymerases..." by adding a PEF protein P45 to a nucleic acid polymerase reaction. However, the specification only provides evidence for the protein P45 enhancing polymerases of the *pyroccocus* species and Vent. Applicant only speculates that the reaction will enhance other polymerases from different species, those known and/or unknown. Contrary, to Applicant's arguments further experimentation is necessary and undue because one skilled in the art cannot readily anticipate the effects of the PEF protein P45 on other polymerases as claimed.

In response to Applicant's arguments that it would not be undue experimentation to test any and all polymerase for activity bases on multiplex assays commonly known in the art, the Examiner respectfully disagree. While the examiner agrees that multiplex screening methodologies are readily available and known in the art, there is a significant lack of predictability in the art for the instant invention. As noted earlier, one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. This is because it is not obvious from the disclosure of the species given in the examples, what other species will work (*be enhanced or controlled by the protein*). Therefore,

the Examiner maintains that undue experimentation is necessary to practice the invention as currently claimed.

6. No claims are allowed. However, the claims are free of the prior art.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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4/24/06